

Exhibit 12

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Intravesical migration of levonorgestrel-releasing intrauterine system (LNG-IUS) with calculus formation

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ABSTRACT

The intrauterine contraceptive device (IUD) has been in use for many years as an effective means of birth control. Migration of the device from the uterus to the pelvic cavity is not uncommon and has been reported previously, however intravesical migration and secondary calculus formation is relatively rare. We report a 28-year-old woman in whom an intrauterine contraceptive device (LNG-IUS) migrated from the uterus to the bladder and resulted in stone formation. This case shows that the newer hormone releasing IUDs may also cause bladder perforation.

KEY WORDS

Mirena[®], Levonorgestrel-releasing intrauterine system (LNG-IUS), Bladder stone, Intrauterine device

INTRODUCTION

Intrauterine contraceptive devices (IUDs) have been in use for more than three decades. Hormone releasing IUDs were developed in the 1970s but it was not until 1995, that the levonorgestrel-releasing intrauterine system (LNG-IUS) became licensed for use in the United Kingdom. Perforation of the uterus by an IUD is reported to occur following 0.2–9.6 per 1000 insertions; however fewer than 2% involve the bladder.¹

Intravesical migration and secondary stone formation has been reported with other IUDs but to our knowledge this is the first reported case of intravesical migration of a LNG-IUS.

CASE REPORT

A 28-year-old woman had a LNG-IUS inserted by an experienced practitioner 6 weeks after vaginal delivery. She had no previous pelvic surgery. The uterus was retroverted and the procedure was initially painful. At 6-week and 1-year reviews, she was asymptomatic and the LNG-IUS threads were visible through the cervix.

Just after her second visit she presented to the urologist with frequency, urgency and supra-pubic discomfort. Urinary tract infection was confirmed and treated accordingly. She failed to attend for an abdominal X-ray but a pelvic ultrasound detected no abnormality in her bladder or pelvis. She did not

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attend a 5-month follow-up urology appointment as her symptoms had completely settled.

Two months following her last visit, her bladder symptoms returned and she requested the LNG-IUS be removed. On attempting removal, the threads of the LNG-IUS were avulsed. At subsequent hysteroscopy the LNG-IUS could not be visualised in the uterine cavity but cystoscopy revealed one limb of the LNG-IUS penetrating the posterolateral bladder wall with an attached calculus (Figure 1). Once the calculus was fragmented with the lithotrite the perforating limb of the IUD started to retract through the bladder wall and was quickly grasped to prevent its loss back into the wall or cavity of the uterus. It was then easily removed by pulling it through the perforation and via the urethra intact. A catheter was removed after 5 days and the patient subsequently voided well with resolution of her symptoms.

DISCUSSION

The LNG-IUS is a T-shaped plastic device containing a reservoir of levonorgestrel, which delivers 20 µg per day over a 5-year period via a rate limiting surface

membrane. It was first licensed in the United Kingdom in 1995.² Pregnancy rates compare favourably with other forms of contraception and the released progestogen reduces uterine bleeding making it useful for managing menorrhagia.

One major problem with IUDs is uterine perforation, which can be complete or partial. Uterine perforation was originally thought to occur at the time of insertion but it has now been realised that migration and erosion can occur at any time and into any structure. Migration has been reported into adjacent structures including the broad ligament, urinary bladder, the peritoneum and more distant structures including the appendix and colon.^{3,4}

Despite the various innovations in the design and delivery of intra-uterine devices it is still not certain whether the newer hormone releasing intra-uterine devices offer any advantage in reducing the incidence of uterine perforation or erosion. The exact mechanism of perforation is currently not entirely known and may well be influenced by other factors like operator experience, position of the uterus and the timing of insertion in relation to the pregnancy.⁵

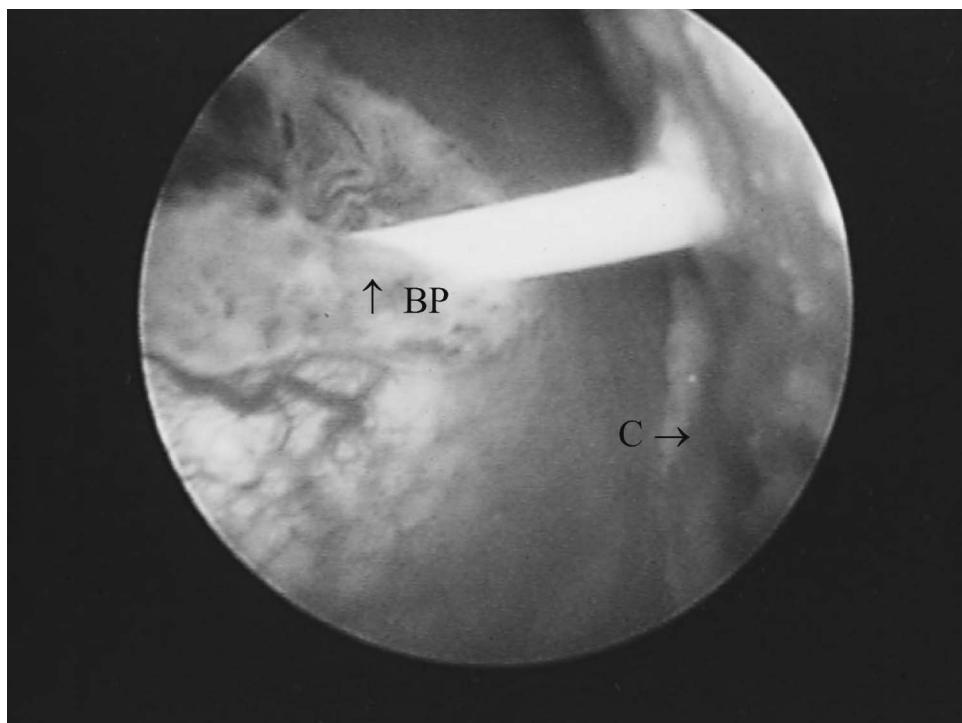


Figure 1 Cystoscopy shows a stone adherent to the limb of the IUD penetrating the posterior wall of the bladder. (BP, bladder perforation; C, calculus)

Our patient developed irritative bladder symptoms and urinary infection 12 months after the insertion of the LNG-IUS. These symptoms resolved but returned later when the stone was detected. It is possible that her original symptoms were simply the result of urinary infection, a common occurrence in a young sexually active woman. Alternatively, her initial symptoms may have been caused by perforation of her bladder by the limb of the LNG-IUS, recurring later with growth of the calculus. This would explain the initial normal pelvic scan. Interestingly, she did not become pregnant during this period because part of the device remained within the uterus or because progestogens were still being released in close proximity to the endometrium providing contraceptive protection.⁶

An IUD, which has migrated into the bladder and stimulated calculus formation, can be removed cystoscopically or via a cystotomy if the calculus cannot be fragmented via the cystoscope. In this case removal was possible at cystoscopy.

As early uterine perforation by an IUD may be asymptomatic, careful post insertion examination and follow up is essential.^{7,8} Whilst in any patient with an IUD who presents with persistent lower urinary tract symptoms, the possibility of intravesical migration of the device must be considered and excluded by investigation, which should include a cystoscopy and pelvic ultrasound scan, even if the threads are normally positioned.

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